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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/766,350	12/13/96	CHATTERJEE M	304142000321

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EXAMINER	
REEVES, J	
ART UNIT	**PAPER NUMBER**
1642	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

3/31/99

Office Action Summary	Application No. 08/766,350	Applicant(s) Chatterjee et al
	Examiner Julie E. Reeves, Ph.D.	Group Art Unit 1642

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-24 and 26-61* is/are pending in the application.

Of the above, claim(s) *6-19, 38, 41, 44-53, 57, and 58* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-5, 20-24, 26-37, 39, 40, 42, 43, 54-56, and 59-61* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5, 6*

☒ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Groups I, IV, V and VI and between Groups I and III in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the methods of using the product should be examined together. This is not found persuasive because the one product can be used for more than one method, as evidenced by the different inventions. Once allowable product claims are identified, then method claims which incorporate all the limitations of the product claims, and which do not present any new issues, may be rejoined.

The requirement between Groups I, IV, V and VI is still deemed proper and is therefore made FINAL.

The restriction between groups I and III has been withdrawn in view of the reasoning set forth in paper no 9.

2. Claims 59-61 have been added. Claim 25 has been canceled. Claims 1-24 and 26-61 are pending. Claims 3-4, 20, 23-25, 37, 39-40, 42-43, 54 and 56 have been amended. Claims 1-5, 20-24, 26, ~~35~~ 37-37, 39-40, 42-43, 54-56 and 59-61 are under examination.

3. This application contains claims 6-19, 38, 41, 44-53, 57-58 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. The application is now in compliance with the sequence requirements.

Specification

5. The disclosure is objected to because of the following informalities: blanks in the text on page 14, line 13 and page 78, line 8. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

6. Claims 21-22, 26, 29-30, 32, 33, and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 26 in indefinite for reciting "wherein the polypeptide contains a region that is homologous to human milk fat globule" because it is not clear what is meant by the word "homologous" nor is it clear how a protein can be homologous to a fat globule. The specification defines homology as " when the amino acid sequences of HMFG and a 11D10 polypeptide are aligned in any manner, including the same or reverse orientation to each other, at least 2, preferably 3, more preferably 4, contiguous amino acids within the polypeptide match with HMFG" (page 24, lines 16-24). This definition differs from the claim recitation because the specification teaches that the four preferable matches would be contiguous. In contrast the claim, as written, recites that the polypeptide which comprises at least one CDR contains a region that is homologous to HMFG. The region which is homologous as recited in the claims, is not limited to an 11D10 region. The open claim language allows for another, non-11D10 portion comprised by the polypeptide to be homologous.

which tandem repeat.

b. The amino acid sequence for HMFG is apparently not known. The Specification teaches that HMFG "has several proteinaceous (and thus antigenic) components. As used herein, it refers to a semi-purified extract of an HMFG-expressing breast cancer cell line, along with antigenically related substances, including HMFG expressed on breast cancer cells and more highly purified purifications" (page 20, lines 12-21). Because the claim does not recite which HMFG sequence, one skilled in the art would not be able to determine the metes and bounds of the claims. maintain

c. Furthermore, it remains unclear what sort of alignment is allowed (i.e., gaps, mismatches) and which amino acid residues are considered to be similar. Further, despite the high level of skill in the genetic analysis art, there remains a lack of development concerning the definition of the word "homology", as evidenced by Lewin (Science 237:1570 (1987)), in which homology is defined as "the inference of common evolutionary origin" (page 1570, last paragraph). In addition, as further evidenced by Reeck et al (Cell V 50:667 1987), homology has a precise meaning in biology of having a common evolutionary origin between two or more things. Thus homology is a concept of quality; amino acid or nucleic acid sequences are either homologous or they are not. It is not clear how the amino acids "match" a HMFG sequence. Does a hydrophilic amino such as Asp in 11D10 "match" a hydrophilic amino acid Lys or Glu in 11D10? One cannot therefore determine what is meant by the phrase "homologous".

d. Claims 21-22 and 33 are indefinite for reciting "a light chain", "a heavy chain" or "a light chain variable region and a heavy chain variable region". From this language it appears

that applicant is referring to one of chains or regions, or that there exists a class of chains or regions, only one of which is being recited in the instant claim, or that the claim is intended to apply to other chains or regions beyond those which are disclosed in the specification. It is not clear that the claims refer to the 11D10 light chain, 11D10 heavy chain, 11D10 light chain variable region and 11D10 heavy chain variable region.

e. Claims 29-30 are indefinite for reciting "IL-2" and "GM-CSF" because it is not readily clear what these abbreviations mean. Full terminology should be in each instance of the claims without the addition use of redundant abbreviation in parentheses or otherwise. Abbreviations render the claim indefinite because the same abbreviation may represent more than one element or concept.

f. Claim 32 is indefinite for reciting "the amino acids of SEQ ID NO: 2 and the amino acids of SEQ ID NO: 4" because it is not clear whether the claim intends to recite that all of the amino acids of SEQ ID NO: 2 and 4 or whether the "at least 10 contiguous amino acids", as recited in dependent claim 31. There is no proper antecedent basis for the term "the amino acids". As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

g. Claim 35 is indefinite for reciting "humanized antibody" because it is not clear what the antibody binds and whether the antibody contains all six 11D10 CDRs. Does claim 35 read upon a humanized anti-IL6 antibody, for example, which comprises one of the CDRs of 11D10? Would the 11D10 CDR replace one of the IL-6 antibody CDRs, fore example, or would

the humanized antibody contain all six IL-6 CDRS and also have as a fusion protein some 11D10 CDR sequences? It is impossible to determine the metes and bounds of the claims.

Deposit of Biological Materials

7. The claims 1-5, 20-22, 26, 27-37, 39, 40, 42- 43, 54, 55, 56, 59-61 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

a. It is unclear if a cell line which produces an antibody having the exact chemical identity of **11D10** is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

b. For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-

determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species **11D10**. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

c. The declaration of filed 10/8/98 as Paper no 13 has been considered carefully but is deemed not to be persuasive. The declaration provides for adequate assurances as to the irrevocable availability of the hybridoma. The declaration states that the hybridoma 11D10 has been deposited with the ATCC on 17 January 1996, before the effective filing date of the instant application.

d. If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b). The declaration of Dr. M. Chatterjee, attachment to paper no 14 filed 10/8/98 has been considered carefully but is deemed not to be persuasive because the declaration has not ben signed. Not Signed. Proper because evid ATCC

8. Claims 20-24, 26, ~~35~~ 27-36, 39, 42, 61, 56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polypeptides which contain all six CDRS of

Maintain 35, 62, 63

11D10, does not reasonably provide enablement for polypeptides which contain only one of the six CDRS. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. Chatterjee et al state the art-recognized experience that for any novel therapy, the transition for the laboratory to the clinic (animal experiments to the bedside) is a quantum leap (Cancer Immunol. Imunother., 1994, see Introduction). Results obtained under controlled conditions and in inbred animals, as in the instant specification where nude mice are used as a test animal, often differ from the clinical response obtained in patients. This applies to strategies drawn to cancer therapy.

c. Although monoclonal antibodies have been shown to have specificity for several tumor antigens, and monoclonal antibodies have been able to induce various degrees of tumor immunity for some diseases, few examples have appeared in the application of autoimmune antibodies as part of immunotherapy to human tumors, it is not clear from the specification

whether autoantibodies can generate antitumor responses to all tumors, in all species and to what degree.

d. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. One skilled in the art would reasonably expect that in order to generate a anti-HMFG immune response, that all six CDR of the anti-idiotypic antibody 11D10 are necessary. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an 11D10 antibody in unspecified order and fused to

any human or nonhuman framework sequence, have the required binding function. Similarly, and taken in view of the teachings of Chatterjee et al, one skilled in the art would reasonably conclude that an polypeptide having no less than all CDRs would be insufficient to generate the proper immune response. The specification provides no direction or guidance regarding how to produce fusion proteins and antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional humanize antibody can be obtained by replacing the CDR regions of an acceptor antibody with the CDRs of a donor antibody. As evidenced by Adair et al. (PCT GB90/02017) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (p. 4). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substiution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

e. Therefore, in view of hte teachings of Panka et al, Rudikoff et al, Adair et al, Amit et al and Chatterjee et al, which support the complexity and unpredictability of the art, in view of the broadly written claims,in view othe insufficient teachings and/or guidance in the specification regarding the use of any 11D10 CDR to illicit the desired response, it appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teachings of the specification.

Claim Rejections - 35 U.S.C. § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> (f) he did not himself invent the subject matter sought to be patented.

10. Claims 1-5, 20-27, 31-33, 36, 37, 39-40, 42-43, 55-56 and 59-61 are rejected under 35 U.S.C. 102(b) as being anticipated by any of

i. Chatterjee Antigen and Antibody Molecular Engineering 1994 (see page 140, Fig 1, for example)

ii. Chatterjee et al Cancer Immunol Immunother 1994 Vol 34 75-82 (See page 77, last full paragraph, for example)

iii. Chakraborty et al Proc Am Assoc Cancer Res 1994 Abstract 2963 (See Abstract); or

iv. Chakraborty et al 1995 J Immunotherapy Vol 18(2) 95-103 (see page 96, col 1 "Antibodies")

a. Claims 1-5, 37, 40, 43, 54, 59-60 recite hybridoma cells designated HB12020, antibody produced thereby, the antibody in a pharmaceutically acceptable excipient, such as saline or PBS, an adjuvant, a kit comprising suitable package, such as a test tube or vial. Claims 20-24, 26, 35-36, 39, 42, 61, 56 recite polypeptide comprising at least one CDR of the heavy or light chain variable region of 11D10. Due to the open claim language comprising, these claims read upon whole 11D10 antibody. Claims 21-24 and 36 recite limitations which are an inherent properties of the 11D10 antibody of the prior art. As evidenced by the specification, the 11D10 antibody has heavy and light chains consisting of SEQ ID NO: 2 and 4. Also the 11D10 antibody has two heavy and two light chains, meeting the limitation of a plurality of polypeptides. It is noted that Section 102(b) contains the clause the invention was "described in a printed publication in this or a foreign country". This invention was clearly described in a publication more than one year prior to the date of application for patent in the United States.

b. The unsigned 1.132 declaration submitted 8 Oct 1998 by M. Chatterjee; K. Foon and S. Chatterjee has been considered carefully but deemed not to be persuasive. The Declaration attempts to overcome a 102(b) rejection by stating that the 11D10 hybridoma and antibody were not publicly available. It is noted that 102(b) also bars inventions which are described in a written publication. Clearly 11D10 has been described in written publications more than a year before the filing of the US application, as evidenced above. Additionally, the declaration are not signed. Thus the rejection is made.

11. Claims 1-5, 20-27, 31-33, 36-37, 39-40, 42-43, 55-56 and 59-61 are rejected under 35 U.S.C. 102(f) as by any of Chatterjee et al (Antigen and Antibody Molecular Engineering 1994), Chatterjee et al (Cancer Immunol Immunother 1994 Vol 34 75-82), Chakraborty et al (Proc Am Assoc Cancer Res 1994 Abstract 2963) or Chakraborty et al (1995 J Immunotherapy Vol 18(2) 95-103 (see page 96, col 1 "Antibodies") because the inventors did not invent the work sought to be patented.

a. Claims have been described above. The instant application lists M. Chatterjee; K. Foon and S. Chatterjee as the sole inventors of the 11D10 antibody.

b. In contrast, Chatterjee et al (Antigen and Antibody Molecular Engineering 1994) lists not only M. Chatterjee and K.Foon; but also lists E. Mrozek; S. Mukerjee; R. Ceriani and H. Kohler as authors on a paper discussing the 11D10 antibody. Similarly, Chatterjee et al (Cancer Immunol Immunother 1994 Vol 34 75-82) lists H. Kohler as an author but not an inventor. Additionally, Chakraborty et al (Proc Am Assoc Cancer Res 1994 Abstract 2963) list as authors, but not inventors, the following: M. Chakraborty, A. Sherratt and K. Ceriani.

c. From the authorship lists recited above, one skilled in the art would reasonably conclude that in addition to M. Chatterjee; K. Foon and S. Chatterjee; the authors M. Chakraborty, H. Kohler, A. Sherratt, Mrozek; S. Mukerjee; R. Ceriani also contributed to the invention. They are not listed as inventors.

d. The unsigned 1.132 declaration submitted 8 Oct 1998 by M. Chatterjee; K. Foon and S. Chatterjee has been considered carefully but deemed not to be persuasive. The declaration

persuasively accounts for the role of Ceriani, Kohler and Sherratt in the invention of 11D10 such that there is no reason to believe that they contributed to the invention of 11D10.

e. The declaration states that Dr. Mrozek was a post-doctoral fellow who participated in the generation of the hybridoma cell line that produced 11D10 (page 3, second full paragraph) . The declaration state that Dr. Mukerjee was a post-doctoral fellow who participated in generating and characterizing 11D10 antibody (pages 3-4, bridging paragraph). The declaration states that Dr. Chakraborty was a post-doctoral fellow who participated in characterizing 11D10 antibody. The declaration states that all three authors were under Dr. Chatterjee's supervision and worked under her direct supervision. The Declaration states that Dr. Chatterjee was the "lead scientist", she was in charge of the laboratory where 11D10 was made; she distributed the antibody and cell line within the lab and maintained strict and exclusive control over the distribution of the 11D10 antibody.

f. The declaration is not persuasive for the following reasons:

i. The declaration fails to describe whatever scientific contribution Dr. Chatterjee may have made in the production and characterization of the 11D10 antibody and hybridoma.

ii. The declaration clearly states that the hybridoma which produces the 11D10 antibody was generated by Dr. Mrozek, that the 11D10 antibody was generated and characterized by Dr. Mukerjee and Dr. Chakraborty. None of these three scientists are named as inventors.

iii. The declarations are not signed.

g. Thus the rejection is made.

12. Claims 20, 22, 24, 26, 33, 34, 35, 36, 39, 42, 56 and 61 are rejected under 35 U.S.C. 102(e) as being anticipated by Gourlie et al (5,808,033, filed 2/93 and issued 9/98).

a. The claims have been described above.

b. Gourlie et al teaches the sequences VRSGA which exactly matches the sequence VRSGA (31-35) consisting of CDR1 of SEQ ID NO: 4. See residues 12-16 of Gourlie et a;'s SEQ ID NO: 3 and MPSRCH sequence printout generated 23 March 1999. Sequence VRSGA is designated as CDR1 of an antibody heavy chain. Gourlie et al teach chimeric antibody which have heterologous constant regions thus meeting the limitations of claim 34. The heavy chain is in a dimer, thus meeting the limitation of claim 36. Thus the limitations of the claims have been met.

13. Claims 20, 21, 23, 26, 33, 34, 35, 36, 39, 42, 56 and 61 are rejected under 35 U.S.C. 102(e) as being anticipated by Bendig et al (5,840,299, filed 11/95 and issued 11/98).

a. The claims have been described above.

b. Bendig et al teach an antibody comprising the sequence MTQSPSSLSAS which exactly matches the amino acid residues 24-34 of SEQ ID NO: 2, CDR 1 of 11D10 light chain. See residues 4-14 of Bendig et al Fig 1A or residues 24-34 of SEQ ID NO: 1 and MPSRCH sequence printout generated 23 March 1999. Bendig et a teach chimeric and humanized

antibodies which contain amino acid residues 24-34 of 11D10. Thus the limitations of the claims have been met.

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Reeves, Ph.D., whose telephone number is (703) 308-7553. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Julie E. Reeves, Ph.D.

Patent Examiner

(703) 308-7553

JULIE REEVES
PATENT EXAMINER